2019 -2020

DELHI PHARMACEUTICAL SCIENCES AND RESEARCH UNIVERSITY

(Incorporating DIPSAR as constituent college as per DPSRU Act)

First DSRC Report

for

Doctor of Philosophy (Ph.D.)

Govt. N.C.T. of Delhi,

Pushp Vihar, Sector-III, M.B. Road,

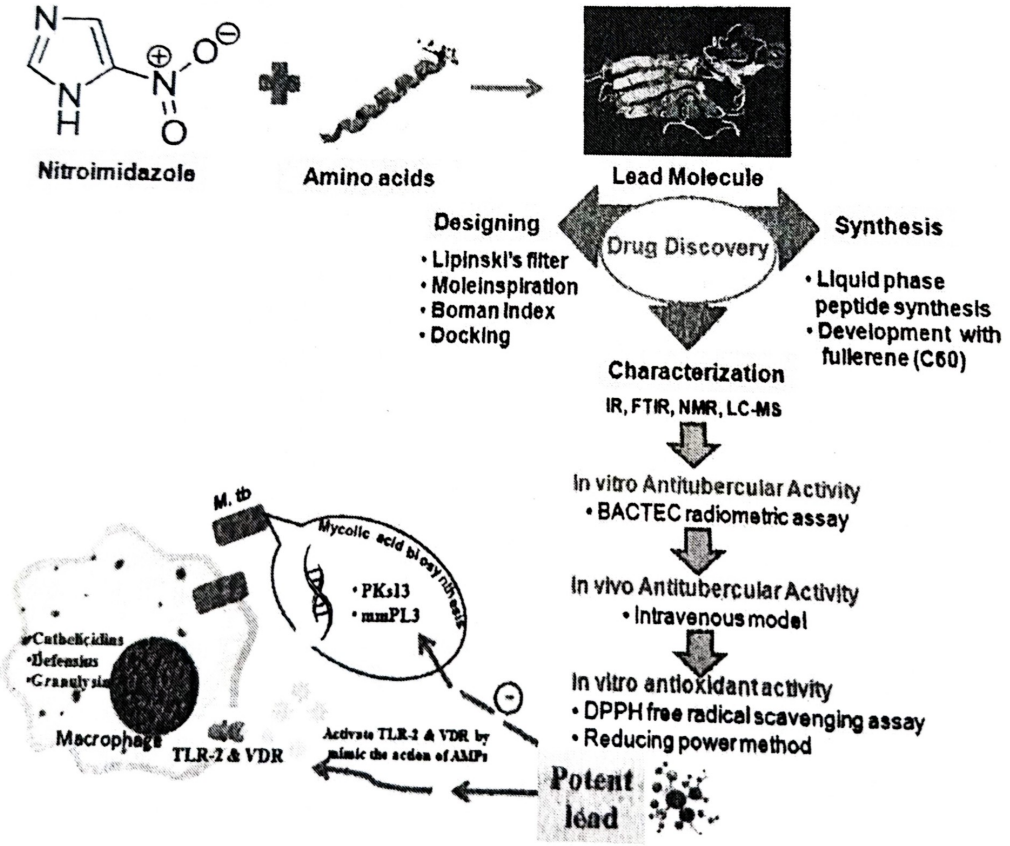
New Delhi-110017

Website: www.dpsru.edu.in

(Approved by UGC under section 2f of UGC Act)

Accreditation by Life sciences Sector Skill Development Council

By targeting naturally synthesized human immune cells associated anti-tubercular peptides namely Cathelicidins; Defensins; Granulysin we would develop new lead molecule, which would mimic the same action more effectively (Fan YL et al, 2018; Adrian FG, 2011). These endogenous peptides contain varying number of amino acids. That's why; here we are proposing all those amino acids that are themselves involved in the better survival strategies to evade phagocytosis process. For example: Defensins are human immune cell derived antitubercular peptides containing 29–35 amino acid residues (cysteine residues) (Okada M et al, 2011; Sancho-Vaello E et al, 2017; Richardson ET et al, 2015). The defensins are major components of the innate immune response against Mtb. It was observed that b-defensins along with L-isoleucine showed enhanced anti-tubercular efficiency [4] and Granulysin enriched with arginine and lysine residues, which shosws anti-tubercular activity by acting upon mycobacterial membranes, leading to the disruption of liposomes and induction of apoptosis. In this view, we would develop new lead molecule targeting against VDR & TLR microphage activation (Ameer K et al, 2016; Okada M et al, 2011; Ann Vu et al, 2016) and distructing Mycolic acid biosynthesis i.e. PKs13 and mmPL3 gene (Marrakchi H et al, 2013; Geetha VR, 2014; Su CC et al, 2019). Interestingly, in this proposal, we are designing and synthesizing small chain peptides using various combination of few amino acids attached to the nitroimidazole, which would act potentially against *Mycobacterium tuberculosis*.



Publication: Sharma P, Nandave M, Goyal RK. A Review: Prevention, Treatment and Management of Tuberculosis through Combinational Approaches of Different Indian Systems of Medicine. Drug Res 2020; 70: 65–70.

Conferences:

1. Poster Presented in 7th International Congress of the Society for Ethnopharmacology, India (SFEC 2020) on the topic "**Formulation of fiber enrich polyherbal palatable cookies for better glycemic control**" from15 to 17 Feburary, 2020, Hamdard, New Delhi.
2. Oral presentation in DPSRU, **international conference on cardiovascular sciences** from 21 to 23 Feb,2020 on the topic "**Impact of fiber enrich polyherbal cookies on blood glucose level: A pilot study in healthy subjects and a cross-over study in subjects with impaired glucose tolerance and metabolic syndrome".**

Signature of Student

Priyanka Sharma

Signature of Supervisor

PART- B

REPORT OF THE DSRCx

Name of the research Scholar: Priyanka Sharma.

Registration No: 08/Ph.D./DPSRU/2019.

Conduct of the Research Scholar.

Progress Report: (Annexure)

Overall Assessment of the progress and specific comments:

1. To do more literature survey for the selection of targets.
2. To ensure work on synthetic antimicrobial peptide.
3. As per an expert, if you choose nitroimidazole for attachment with sequencing of amino acids then that moiety will not be considered as peptides.
4. A Selection of in-vitro activity should be updated as per current literature.
5. Before doing in-vivo, make sure of the availability of BS3 facility.
6. It is suggested to change the Ph.D topic, due to unavailability of BS3 facility.

[redacted]

28/04/21

(Expert 1) (Expert 2) (Supervisor) (Co-Supervisor)

Dr. URVASHI SINGH, MD, PhD
Professor
Department of
All India Institute of
Ansari Nagar, New Delhi-110029

Date:

DELHI PHARMACEUTICAL SCIENCES & RESEARCH UNIVERSITY
(Incorporating DIPSAR as Constituent College as per DPSRU Act)

Second DSRC Report
for
Doctor of Philosophy (Ph. D)

Govt. of N.C.T. of Delhi,
Pushp Vihar, Sector – III, M.B. Road,
New Delhi-110017
Website: www.dpsru.edu.in
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Accreditation by Life Sciences Sector Skill Development Council

PART – A

PROFORMA FOR HALF-YEARLY PROGRESS REPORT OF REGISTERED RESEARCH SCHOLARS FOR THE PERIOD ENDING JANUARY 2020 PROGRESS REPORT FROM AUGUST 2019 TO JANUARY 2022

1. Name of Research Scholar: Priyanka Sharma
2. Correspondence Address: Prabha electricals 5/136 banna devi G.T road Aligarh
3. Contact No. 9910621497
4. Email: sharmapriyanka21992@gmail.com
5. Regn. No.08/PhD/DPSRU/2019
6. Date of Regn. 14/10/2019.
7. Semester Fee deposited**: Rs. 30385/- Vide R. No. PH/ADMISSION/DPSRU/ Dated: 10/12/2018
8. Approved Topic of Research: Development and Evaluation of Antidiabetic Formulation by Targeting GPCRS in Diabetes-Associated NAFLD: In silico In vitro, and In Vivo Approach
9. Nature of Fellowship, if any: Yes (attached)
10. Details of leaves availed during the period under report, if any
    Yes
11. *Research work done during the period:

1. Evaluation of Preliminary Work
   - Objective
   - Methodology
   - Preliminary Results
2. Institutional Animal ethical committee approval: Yes (attached)

12. Research papers published:
13. * Any other information not covered above:

- One day symposium attended on **Metabolic Associated Fatty Liver Disease** on 25th June, 2022 at **Translational Health Science and Technology Institute (THSTI),** Faridabad.
- The ICMR has approved this project **(file no 17x(3)/Adhoc/71/2022-ITR).**
- **Reason: Delaying 2nd DSRC: -**
  Due to **global pandemic** and my **maternity leaves** from 23rd Nov '2020 to 23rd August'2021,

Date: 25/7/22 (Name/Signature of the Research Scholar)

*Attach separate sheets, if required, for details. **Attach photocopies of University Cash Receipt as proof of semester fee deposited.

25/7/22

Countersignature of Supervisor

Executive Summary (2nd DSRC)

Name of Research Scholar: Priyanka Sharma **Name of Supervisor:** Dr. Mukesh Nandave

Registration No.: 08/PhD/DPSRU/2019 **Date of DSRC:** 20th Aug'2022

Title of thesis (Initial): Design, Synthesis and Development of Small Chain Peptidomimetics for Treatment of Tuberculosis

Title of thesis (Modified): Development and Evaluation of Antidiabetic Formulation by Targeting GPCRS in Diabetes-Associated NAFLD: In silico In vitro, and In Vivo Approach

Abstract of work done (200-300 words, in structured manner with separate paragraphs for Introductionending with Objectives; Methodology; Results; Conclusions and Proposed further work with expected outcomes):

Introduction: Obesity, type 2 diabetes (T2D), and non-alcoholic fatty liver disease, recently known as metabolic dysfunction-associated fatty liver disease (MAFLD), have been increasing at an alarming rate, with an estimated prevalence of 25.2%, with 50% of diabetic patients at higher risk due to the 2- or 3-fold risk of developing end-stage liver disease and hepatocellular carcinoma (HCC)

Objectives: To screen major phytoconstituents via in silico study and confirm their presence in hydroalcoholic extract of plants *Picrorhiza Kurroa, Phyllanthus niruri*, and *Tinospora cordifolia* through characterization methods.

Methodology and results: In this study, 49 major phytoconstituents (chosen from twenty-two chemical constituents of T. cordifolia, eleven chemical constituents of P. niruri, and sixteen chemical constituents of P. kurroa) were molecular docked against GPR120 and GPR40. The binding interactions of best 6 docked chemical constituents against GPR120 and GPR40 were studied. Physiochemical characterization of all three plants was done. Further, all three plants in maceration extraction technique methanol gave the highest value percentage yield. In addition, six phytoconstituents with the highest binding docked score were identified and characterized from combined extract using HPLC, LC-MS, and MS-MS. Our study results showed that phytoconstituents Cinnamic acid, Veronicoside from P. kurroa, Corilagin, Caffeic acid from P. niruri and malic acid, and ferulic acid from T. cordifolia had high affinity for GPR120 and GPR40 by interacting at the receptor's catalytic site.

Expected outcomes: Our ongoing in vitro and in vivo studies of these phytoconstituents in experimental models of T2D with MAFLD are sincere efforts to find out insulin-sensitizing agent for the treatment of T2D.

Work Status:

S. No	Work	Status
1.	In silico study of various bioactive compounds of T. cordifolia, P. niruri, & P, Kurroa	Done
2.	Authentication, extraction & standardization of raw material of T. cordifolia, P. niruri, & P, Kurroa	Done
3.	Characterization and identification of specific phytoconstituents from the plant extract	Done
4.	In vitro screening of lead compounds for activation of GPR120 and GPR40	Within next 6 months

Recommendations of 1st DSRC	Compliance of 1st DSRC (write clearly what changes were done)
1. To do more literature survey for the selection of targets. 2. To ensure work on synthetic antimicrobial peptide. 3. As per an expert, if you choose nitroimidazole for attachment with sequencing of amino acids then that moiety will not be considered as peptides. 4. A Selection of in-vitro activity should be updated as per current literature. 5. Before doing in-vivo, make sure of the availability of BS3 facility. 6. It is suggested to change the Ph. D topic, due to unavailability of BS3 facility.	As suggested, the topic of PhD was changed

Recommendations of URAC after 1st DSRC	Compliance
The summary is not well prepared. Lack of uniformity is the main problem. Throughout the report in vitro and in vivo were written in different ways. Many references are cited in the report but only 4 or 5 are listed, those references were also not listing using a uniform style.	The revised protocol was submitted

Recommendations of 2nd DSRC:

1. Adding the GVSA value to the final docking score provides strong justification.
2. A quantitative graph with details should be included as well.
3. Schematic representation of protein should also be added.
4. To write a review article in which the selected targets are mentioned, which has been investigated and has not been done, why?
5. NAFLD's pathophysiology must be reviewed again to ensure that no further failures occur.
6. The location of the chosen target must also be considered in order to reduce the likelihood of adverse and side effects.

Priyanka Sharma
22/Aug/2022

Signature of Student

22/8/2022

Signature of Supervisor

Dr. Mukesh Nandave
Associate Professor
School of Pharmaceutical Sciences
(I.P. College of Pharmaceutical Sciences & Research of University
... of NCT of Delhi), New Delhi-110017

SRC (write clearly what
f PhD was changed

PART - B

REPORT OF THE DSRC

Name of the Research Scholar: Priyanka Sharma

Registration no.: 08/PhD/DPSRU/2019

Conduct of the Research Scholar:

Progress Report: (Annexure I)

Overall Assessment of the progress and specific comments of the Supervisor:

1. Adding the GVSA value to the final docking score provides strong justification.
2. A quantitative graph with details should be included as well.
3. Schematic representation of protein should also be added.
4. To write a review article in which the selected targets are mentioned, which has been investigated and has not been done, why?
5. NAFLD's pathophysiology must be reviewed again to ensure that no further failures occur.
6. The location of the chosen target must also be considered in order to reduce the likelihood of adverse and side effects.

Experts1-

Dr. Shailendra Asthana
Drug Discovery Research Center, **THSTI**.

Experts 2-

Dr. Urvashi B. Singh
Department of Microbiology, **AIIMS**

Supervisor 25/7/22

Dr. Mukesh Nandave
Head of Department of Pharmacology, **DPSRU**

Date: 25/7/22

Executive Summary for URAC for Third DSRC Progress Report

Name of Research Scholar: Priyanka Sharma.
Registration number of Research Scholar: 08/Ph.D./DPSRU/2019.
Name of Supervisor: Dr. Mukesh Nandave
Title of Thesis: Development and Evaluation of Antidiabetic Formulation by Targeting G protein-coupled receptors in Diabetes-associated Non-Alcoholic Fatty Liver Disease: In silico, In vitro, and In vivo Approach.

Abstract of work done:

Introduction: Non-alcoholic fatty liver disease (NAFLD) is a prevalent liver condition often associated with diabetes, characterized by excessive fat accumulation in the liver. The interrelation between diabetes and NAFLD involves complex metabolic pathways, where G-protein coupled receptors (GPCRs) play a significant role. This study focuses on the development and evaluation of an antidiabetic formulation targeting GPCRs to manage diabetes-associated NAFLD.

Objectives: To identify bioactive compounds that can modulate GPCRs involved in the pathophysiology of diabetes and NAFLD from hydroalcoholic extract. The study aims to validate these compounds through in silico and in vitro approaches.

Methodology: The study was conducted in several phases. Initially, network pharmacology was used to analyze the best leads associated with protein targets, elucidating their roles in diabetes and NAFLD pathways. Subsequently, the isolation and purification of two compounds from the combined extract of plant *Tinospora cordifolia* (TC), *Phyllanthus niruri* (PN), and *Picrorhiza kurroa* (PK) using column chromatography were performed. The methodology included developing and optimizing HPTLC for three bioactive compounds. In vitro screening of lead compounds was conducted using ERK phosphorylation, GLP-1 secretion, and insulin secretion assays in relevant cell lines.

Results: The in-silico studies identified six potential compounds—cinnamic acid, ferulic acid, caffeic acid, veronicoside, corilagin, and malic acid—with strong binding affinities to GPR40 and GPR120. ADME analysis confirmed the drug-likeness of these compounds. The isolation and purification processes successfully yielded significant amounts of the target compounds. In vitro, assays demonstrated significant activation of ERK phosphorylation and increased GLP-1 secretion by veronicoside and ferulic acid at 100 μM concentrations.

Conclusions: The study successfully identified and validated bioactive compounds that modulate GPCRs implicated in diabetes and NAFLD. The antidiabetic formulation developed from these compounds showed promising results in in vitro models, suggesting potential therapeutic benefits for managing diabetes-associated NAFLD.

Proposed Further Work: In-vivo evaluation of the most effective test drug in an animal model of diabetes based on a high-fat diet.

Expected Outcomes:

- Comprehensive understanding of the role of GPCRs in diabetes-associated NAFLD.
- Development of an effective antidiabetic formulation with dual benefits for diabetes and NAFLD.

- Successful in vivo studies demonstrated marked improvement in insulin secretion and reduction in liver fat accumulation.
- Successful translation of in vitro and in vivo findings to clinical settings

List of Publications (original research paper or Review), conference presentations, and awards out of the PhD project (Proofs to be attached as annexure):

- Sharma P, Nandave M, Nandave D, Yadav S, Vargas-De-La-Cruz C, Singh S, Tandon R, Ramniwas S, Behl T. **Reactive oxygen species (ROS)-mediated oxidative stress in chronic liver diseases and its mitigation by medicinal plants.** Am J Transl Res Oct 15; 2023.
- Priyanka Sharma, Mukesh Nandave, Anoop Kumar (2024). **Reporting of ADRs Across the Globe: India, USA, EU, and Non-EU in Pharmacovigilance Essentials Advances, Challenges and Global Perspectives. Editors: Mukesh** Nandave, Anoop Kumar, Springer, Pages 127-146
- Priyanka Sharma, Mukesh Nandave, Kalicharan Sharma (2023). Computational approaches in drug discovery and design, In **Computational Approaches in Drug Discovery, Development and Systems Pharmacology.** Editors: Rupesh Kumar Gautam, Mohammad Amjad Kama, Pooja Mittal, Elsevier, Pages, ISBN 0323993737, 9780323993739.
- Efficacy of oral hypoglycemic agent in diabetes associated with Non-alcoholic fatty liver disease: A systemic review and Meta-analysis **(Communicated)**

Conference presentation:

- Attended Joint Annual Meeting of International Society for Heart Research & International Academy of Cardiovascular Science at **AIIMS**, Jodhpur, from February16-18, 2024
- Priyanka Sharma, Mukesh Nandave. Research paper presented verbally in **Advances in Cardiovascular Medicine and Research (ACMR-2023) on** the topic at PGIMER, ***Potential of Ayurveda Botanicals in Diabetes Associated with Nonalcoholic Fatty Liver Disease*** Chandigarh, from February 16–18, 2023.
- Priyanka Sharma, Mukesh Nandave, Pradeep Kumar Prajapati. Research paper presented verbally in **9th World Ayurveda Congress & Arogya Expo 2022** on the topic **"Potential of Ayurveda botanicals in diabetes associated with nonalcoholic fatty liver disease"** at Kala Academy, Panjim, Goa, from 8th to 11th December, 2022

Recommendations of 2nd DSRC	**Compliance of 2nd DSRC (write clearly what changes were done)**
1. Adding the MM-GBSA value to the final docking score provides strong justification. 2. A quantitative graph with details should be included as well. 3. A schematic representation of the protein should also be added. 4. NAFLD's pathophysiology must be reviewed again to ensure that no further failures occur.	MM-GBSA value and quantitative graph hav been added to the study.

5. The location of the chosen target must also be considered in order to reduce the likelihood of adverse and side effects.	

Recommendations of URAC after 2nd DSRC	Compliance
The modified title is complicated and n understandable	The revised protocol was submitted
Write full form of GPCRs in the tittle	
The plant species names to be written carefully	
In expected outcomes, use of "sincere efforts" wrong	
DSRC recommendations should also be writte correctly	

Recommendations of 3rd DSRC:

- In Network Pharmacology, create networks by breaking them down with selected protein targets.
- In cell line studies, reduce the concentration from 100mM.
- Add a mechanistic approach of lead compounds with the target in schematic form to the presentation.
- Include structures to differentiate each compound, showing the effects on response due to the addition or subtraction of functional groups or bonds.

Signature of Student

21/6/24

Signature of Supervisor

Dr Mukesh Nandwana

Executive Summary for URAC for Forth DSRC Progress Report

Name of Research Scholar: Priyanka Sharma.
Registration number of Research Scholar: 08/Ph.D./DPSRU/2019.
Name of Supervisor: Dr. Mukesh Nandave
Title of Thesis: Development and Evaluation of Antidiabetic Formulation by Targeting G protein-coupled receptors in Diabetes-associated Non-Alcoholic Fatty Liver Disease: In silico, In vitro, and In vivo Approaches.

Abstract of work done:

Introduction: Diabetes and non-alcoholic fatty liver Disease (NAFLD) are interconnected metabolic disorders with severe health implications. Current treatments are often limited in their efficacy, necessitating the exploration of novel therapeutic strategies. The study evaluates the therapeutic potential of a three herbal polyherbal formulation (Tinospora cordifolia, Phyllanthus niruri, Picrorhiza kurroa) in managing diabetes and NAFLD using an in vivo model.

Objective: To assess the efficacy and synergistic effects of the polyherbal formulation and its active phytoconstituents in regulating metabolic markers, improving liver function, and reducing pancreatic damage in a high-fat diet (HFD)-induced diabetes-NAFLD model.

Methodology: A total of 42 Wistar rats were divided into seven groups, including a Salin control, HFD diseased control, and treatment groups receiving Sitagliptin (10 mg/kg), polyherbal extract (200 mg/kg and 400 mg/kg), and key active compounds namely, veronicoside (50 mg/kg) and Ferulic acid (50 mg/kg). Diabetes and NAFLD were induced using a HFD regimen over 8-10 weeks. Treatment was administrated for 14 weeks, followed by biochemical analyses (glucose, lipid profile, liver enzymes), insulin tolerance test (ITT), oral glucose tolerance tests (OGTT), and histopathological examinations of liver and pancreatic tissues.

Results: The polyherbal extract, particularly at 400 mg/kg, significantly improved metabolic markers by reducing cholesterol, LDL, triglycerides, and free fatty acids while increasing HDL levels. Liver function markers (AST, ALT) improved, with histological findings confirming reduced fibrosis and inflammation. The formulation also showed protective effects against pancreatic damage. Notably, Ferulic acid demonstrated the most significant liver-protective effects, while veronicoside improved glucose metabolism and insulin sensitivity.

Conclusion: The polyherbal formulation and its key active phytoconstituents exhibited promising therapeutic potential in managing diabetes and NAFLD by improving metabolic, liver, and pancreatic health. These findings suggest their potential application as alternative or complementary therapies for metabolic disorders.

Proposed Further Work: A clinical study can be proposed to evaluate the therapeutic potential of the most effective test drug in patients suffering from fatty liver and those dependent on insulin, aiming for better therapeutic outcomes.

Expected Outcomes:

- Comprehensive understanding of the role of GPCRs in diabetes-associated NAFLD.

- Development of an effective antidiabetic formulation with dual benefits for diabetes and NAFLD.
- Successful in vivo studies demonstrated marked improvement in insulin secretion and reduction in liver fat accumulation.
- Successful translation of in vitro and in vivo findings to clinical settings

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- Efficacy of oral hypoglycemic agent in diabetes associated with Non-alcoholic fatty liver disease: A systemic review and Meta-analysis **(Communicated)**

PATENT:

Sr. No.	Title of the patent	Innovators	Applicants	status
1	Herbal Composition For Treatment Of Diabetes Associated With Non-Alcoholic Fatty Liver Disease	Mukesh Nandave and Priyanka Sharma	Delhi Pharmaceutical Sciences and Research University (DPSRU) Indian Council Of Medical Research (ICMR)	Patent is drafted and to be filed by ICMR

onference presentation:

- Attended Joint Annual Meeting of International Society for Heart Research & International Academy of Cardiovascular Science at **AIIMS**, Jodhpur, from February16-18, 2024
- Priyanka Sharma, Mukesh Nandave. Research paper presented verbally in **Advances in Cardiovascular Medicine and Research (ACMR-2023) on** the topic at PGIMER, **Potential of Ayurveda Botanicals in Diabetes Associated with Nonalcoholic Fatty Liver Disease** Chandigarh, from February 16–18, 2023.

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Recommendations of 3rdDSRC	**Compliance of 3rd DSRC (write clearly what changes were done)**
☐ In Network Pharmacology, create networks by breaking them down with selected protein target ☐ In cell line studies, reduce the concentration from 100mM. ☐ Add a mechanistic approach of lead compounds with the target in schematic form to the presentation. ☐ Include structures to differentiate each compound, showing the effects on response due to the addition or subtraction of functional groups or bonds.	☐The networks have been refined by breakin them down with selected protein targets ☐A schematic representation illustrating th mechanistic action of lead compounds has bee incorporated ☐The structures of each compound have bee included to highlight their differences, showin how the addition or removal of function groups or bonds influences the biologic response.

Recommendations of URAC after 3rd DSRC	**Compliance**

Recommendations of 4th DSRC:

1. In the final screening, the synergistic effect of the polyherbal formulation, along with the efficacy of the active phytoconstituent from Group 7, is noticeable. This should be considered for further study in the lab for the future.
2. The presentation contains typographical errors that need to be corrected before the thesis defense.
3. According to experts, the work is sufficient and satisfactory.

Signature of Student

Signature of Supervisor